Organophosphate Toxicity

Organophosphates (insecticides, nerve agents) are potent acetylcholinesterase inhibitors capable of causing severe cholinergic toxicity following cutaneous exposure, inhalation, or ingestion. Poisoning is caused by the accumulation of ACh at muscarinic & nicotinic synapses, not by the organophosphate itself. Toxicity generally results from accidental or intentional ingestion of, or exposure to, agricultural pesticides, contaminated fruit, flour, or cooking oil, and wearing contaminated clothing,

ANESTHETIC CONSIDERATIONS:

- Avoid self-contamination while treating patients (neoprene gloves/ gown, charcoal cartridge mask)
  - All patients need aggressive decontamination (clothing removal, irrigation of affected areas)
- Acute respiratory failure is the primary cause of death & is mediated by:
  - bronchorrhea, bronchospasm, diaphragm weakness/paralysis, inhibition medullary resp center
  - Intubation may be necessary for airway control & adequate oxygenation
- Avoid using succinylcholine as prolonged paralysis may result (SCh degraded by AChE)
- Treatment involves three steps:
  - an anticholingergic drug to counteract the acute cholinergic crisis (atropine)
  - an 'oxime' drug to reactivate inhibited acetylcholinesterase (pralidoxime)
  - an anticonvulsant drug to prevent or treat seizures (benzodiazepine)

ANESTHETIC GOALS:

- Reverse acute cholinergic crisis with Atropine 2 mg IV q5-10min until pupil dilation, HR > 80 & ventilation improves (*Miller 7th, Co-existing*)
- Reactivate the function of acetylcholinesterase with Pralidoxime 600 mg IV (*Co-existing*) or 15-30 mg/kg IV/IM over 20 min for adults & peds – may repeat after 4hrs (or 1hr if paralysis worsening) (*Miller 7th*)
- Prevent/treat seizures with Diazepam or Midazolam as needed
- Supportive care

HISTORY

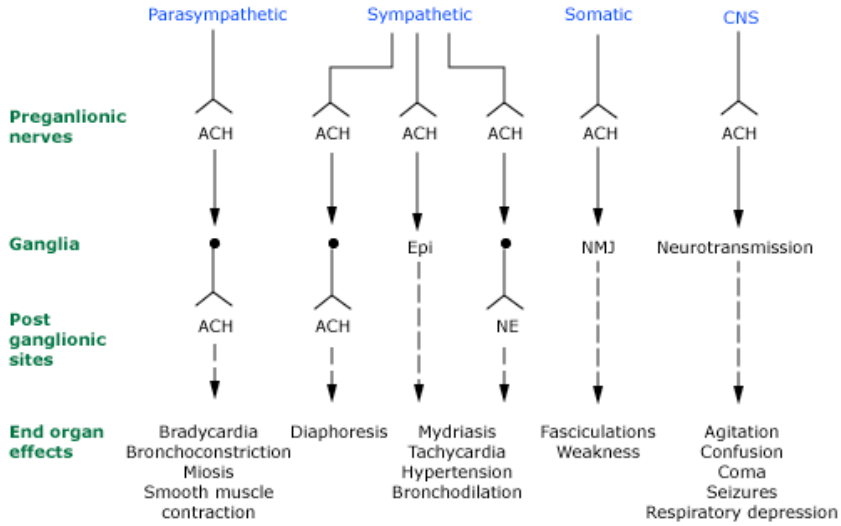
- Organophosphorous nerve agents (eg, tabun [GA], sarin [GB], soman [GD]) were developed in Germany during the 1940s, but were not used for military purposes
  - Most likely agent to encounter is Sarin (isopropyl methyl phosphonofluoridate)
- In addition to potential military or terrorist applications, OPs have been used as insecticides for the past 50 years.
- Their use has declined in the last 10 to 20 years, in part due to the development of carbamate insecticides, which are associated with similar toxicities.
- Medical applications of OPs and carbamates include reversal of NMB (neostigmine, pyridostigmine, edrophonium) and treatment of glaucoma, myasthenia gravis, and Alzheimer disease (echothiophate, pyridostigmine, tacrine, and donepezil)
- OPs are pale yellow to colorless, odorless, & soluble in water where they undergo slow hydrolysis
- Route of absorption – skin or respiratory tract – most severe effects after inhalation
  - Can penetrate clothing, leather, latex rubber etc. (neoprene gloves more resistant)
- Interaction of OPs with AChE is irreversible after a certain time depending on the nerve agent.
  - Formation of an irreversible complex is known as 'aging' & each agent has an aging $t^{1/2}$
  - After 5 half-lives >95% AChE has 'aged' and cannot be reactivated so has important consequences on window of clinical opportunity for treatment.

PHYSICAL

- Diagnosis is made on clinical grounds: clinical features of cholinergic excess should indicate the possibility of organophosphate poisoning.

Muscarinic Effects:
Glandular hypersecretion – salivary, bronchial, lacrimal, sweating, diarrhea etc.
Cardiac – bradycardia, AV block, Q-T prolongation
Bronchospasm
Miosis
Nicotinic Effects:
Skeletal muscle fasciculations, weakness, paralysis
CNS Effects:
Seizures
Coma
Central Apnea

Neurologic effects of organophosphate and carbamate agents



ACH: acetylcholine; Epi: epinephrine; NE: norepinephrine; NMJ: neuromuscular junction.

Overview of organophosphate and carbamate toxicity

References ☑ Graphics ☑

To obtain emergent consultation with a medical toxicologist, call the United States Poison Control Network at 1-800-222-1222, or access the World Health Organization's list of international poison centers (www.who.int/ipcs/poisons/centre/directory/en).

Clinical Syndromes
Acute Toxicity
Generally manifests in minutes to hours
Evidence of cholinergic excess
SLUDGE = Salivation, Lacrimation, Urination, Defecation, Gastric Emptying
BBB = Bradycardia, Bronchorrhea, Bronchospasm
Respiratory insufficiency can result from muscle weakness, decreased central drive, increased secretions, and bronchospasm
Intermediate Syndrome
Occurs 24-96 hours after exposure
Bulbar, respiratory, and proximal muscle weakness are prominent features
Generally resolves in 1-3 weeks
Organophosphorous Agent-Induced Delayed Peripheral Neuropathy (OPIDN)
Usually occurs several weeks after exposure
Primarily motor involvement
May resolve spontaneously, but can result in permanent neurologic dysfunction

INVESTIGATIONS

Diagnostic Evaluation of Acute Toxicity
Atropine challenge if diagnosis is in doubt (1 mg IV in adults, 0.01-0.02 mg/kg in children)
Absence of anticholinergic signs (tachycardia, mydriasis, decreased bowel sounds, dry skin) strongly suggests poisoning with organophosphate or carbamate
Draw blood sample for measurement of RBC acetylcholinesterase activity to confirm diagnosis

A Direct measurement of RBC acetylcholinesterase (RBC AChE) activity provides a measure of the degree of toxicity. Sequential measurement of RBC AChE activity (if rapidly available) may also be used to determine the effectiveness of oxime therapy in regeneration of the enzyme

TREATMENT

See anesthetic goals section above for specific doses from Miller and Co-existing.
Uptodate Table is included below…

Atropine's antagonistic action against ACh at the muscarinic synapses allows control of the muscarinic effects of nerve agents (eg. bradycardia)
Atropine does not bind to nicotinic receptors so it is ineffective in treating neuromuscular dysfunction

Oximes (Pralidoxime, Obidoxime) are compounds capable of reactivating the OP-AChE complex (cholinesterase reactivating agents)
Clinically, oximes reverse actions of the OP at the nicotinic receptor and reduce degree of paralysis
NB: Pralidoxime should not be administered without concurrent atropine, to prevent worsening symptoms due to transient oxime-induced acetylcholinesterase inhibition

Treatment of Acute Toxicity
Deliver 100 percent oxygen via facemask; early intubation often required; avoid succinylcholine
Atropine 2-5 mg IV bolus (0.05 mg/kg IV in children)
Escalate (double) dose every 3-5 minutes until bronchial secretions and wheezing stop
TACHYCARDIA AND MYDRIASIS ARE NOT CONTRAINDICATIONS TO ATROPINE USE;
Hundreds of milligrams may be needed over several days in severe poisonings
Pralidoxime (2-PAM) 2 g (25-50 mg/kg in children) IV over 30 minutes
Continuous infusion at 8 mg/kg/hour in adults (10-20 mg/kg/hour in children)
Benzodiazepine therapy
Diazepam 0.1-0.2 mg/kg IV, repeat as necessary if seizures occur

NB: if you want to read about pyridostigmine pretreatment as a novel military approach to prophylaxis against nerve agent poisoning look in Miller 7th ed, Ch 74: Pg 2341-2.

REFERENCES

Uptodate
Co-existing 5th ed. Pg 551-2
Miller 7th ed. Pg 2338-42